REMARKS

Claims 1, 4-7 and 29-42 are the claims pending and currently under examination in this case. Claims 2-3 and 8-28 have been canceled. Claims 1, 4-7 and 29-42 stand rejected under 35 U.S.C. §103(a) over various references cited by the Examiner.

Remarks Directed to Rejection of Claims 1, 5-7, 29-30, 32-36 and 38-40 Under 35 U.S.C. §103(a) over Grilli et al. in view of Bakhshi et al. and Myseros et al.

With regard to the rejection under 35 U.S.C §103 (a) over Grilli et al. (WO 98/20864) in view of Bakhshi et al. (*Journal of Neuro-Oncology*, 26, 133-9), Applicant hereby incorporates remarks made in conjunction with the combination of these two references in Applicant's communication of October 27, 2005. In particular, Applicant submits that the rejected independent claims 1, 29 and 36 and those that depend therefrom are not obvious over Grilli et al. in view of Bakhshi et al. on the basis that there is no reasonable expectation of success given the teachings of these prior art references and that, therefore, a *prima facie* case of obviousness has not been established. Applicant further submits that the additional citation of the Myseros et al. reference does not supplement the teaching lacking in Grilli et al. and Bakhshi et al.

Grilli et al. is cited as teaching "the treatment of Alzheimer's disease through the use of NSAIDs" (Office Action July 28, 2005, page 3) and that "neuronal damages (i.e. neurotrauma or neuronal injury) related to Alzheimer's disease are specifically taught as treatable by the NSAIDs disclosed therein." (Office Action July 28, 2005, page 3 citing page 6 of Grilli et al.). It is further asserted that "cranial and spinal traumas are also taught to be treatable by the methods disclosed." (Office Action July 28, 2005, page 3 citing page 6 of Grilli et al.).

Bakhshi et al. is cited to bolster Grilli et al. through a teaching of drug administration to the CNS for the treatment of Alzheimer's disease via intrathecal catheter "... alleviating adverse

systemic effects associated with the administration of the drug, ensure adequate blood-brain barrier penetration, etc., as taught by Bakhshi et al." (Paper No. 20050721, page 4, paragraph 1).

The passage apparently cited by the Examiner in the Grilli et al. reference (page 6) states that "[i]t has been found that such non-steroidal anti-inflammatory compounds are particularly suitable for use in the prevention of glutamate receptor-mediated neuronal damages related to Alzheimer's disease ... cranial and spinal traumas ...". Applicant submits that Grilli et al. provides evidence that pretreatment of cultured cells with a non-steroidal anti-inflammatory compound protects some cells from glutamate receptor mediated injury. For example, the Grilli et al. specification details cultured cell exposure to a glutamate receptor agonist, NMDA, whereupon some cells "became acutely necrotic: they exhibited highly swollen cytoplasm containing large vacuoles, nuclear shrinkage and focal clumping of chromatin." (Grilli et al., page 9, line 30 – page 10, line 2). The Grilli et al. specification goes on to describe that *in vitro* "application of ASA preserved hippocampal cell viability from the NMDA-mediated injury." (Grilli et al., page 10, lines 3-5). Further experiments describe the protective effects of NSAIDs on cultured cells exposed to glutamate where "ASA and/or NaSal were added to the chamber 2 min before glutamate exposure." (Grilli et al., page 11, lines 9-10). Thus, Grilli et al. extensively describes protection of cells using NSAIDs.

As Bakhshi et al. only teaches Alzheimer's disease as the indication for intrathecal drug delivery, the limitations of Grilli et al. are not bolstered by Bakhshi et al. with respect to treatment of neurotrauma as claimed.

In the current Office Action, it is again asserted that page 6 of the Grilli et al. specification describes "neuronal damages (i.e. neurotrauma or neuronal injury) related to Alzheimer's disease are specifically taught as treatable by the NSAIDs disclosed therein." It is also again asserted that

"[g]enerally, cranial and spinal traumas are also taught to be treatable by the methods disclosed (p.6)."

Applicant reiterates that page 6 of the Grilli et al. reference describes non-steroidal anti-inflammatory compounds as "particularly suitable for use in the prevention of glutamate receptor-mediated neuronal damages related to Alzheimer disease . . . cranial and spinal traumas . . ." as well as many other conditions. As Applicant noted previously, the Grilli et al. specification only describes instances of pre-treatment of cells in order to protect the cells from glutamate receptor-mediated neuronal damage.

The new citation of the Myseros et al. reference further emphasizes Applicant's position that one of skill in the art would have no expectation of success given the combined teachings of the references.

Myceros et al. is cited as teaching "that prevention and/or treatment of glutamate neurotoxicity (specifically by glutamate antagonists) results in improvement in both mortality and morbidity of patients." The Examiner cites several passages in which it is asserted that Myseros et al. teach that various aspects of injury occur following traumatic brain events. In particular, the Examiner asserts that "[o]n page 263, Myseros et al. teach that diffuse axonal injury is a process that does not occur instantaneously after traumatic brain event, but rather that after impact an immediate and massive release of neurotransmitters (including glutamate) is noted and structural axonal destruction occurs later." (Emphasis added) The Examiner further states that "...Myceros et al teach, on page 264, that the structural axonal lesions seen after sheer injury may both be caused by a mechanical process, but by a failure of ionic homeostasis mediated via the glutamate channel." However, Applicant notes that this reference appears to teach that such damage is prevented by administering glutamate receptor antagonists prior to neurotrauma.

For instance, although it is asserted that "on page 265, Myseros et al. teach that treatment of rats with a glutamate antagonist in the fluid percussion model (an animal model for traumatic brain impact and associated diffuse axonal injury) results in dose-dependent improvement in both mortality and memory and motor tasks," Applicant notes that the apparently cited passage states that "treatment with NMDA antagonists, both with MK-801 and the competitive agonist CGS 19755, before FPI [Fluid Percussion Injury] results in dose-dependent improvement in both mortality (severe FPI) and memory and motor tasks (moderate FPI)." Thus, a protective effect of such compounds appears to be described.

Furthermore, even if Myceros et al. described administration of glutamate receptor antagonists having a therapeutic effect when administered following FPI, this would not ameliorate the lack of a teaching in these references that administration of NSAIDS can be performed with therapeutic effect following the immediate release of excitotoxic neurotransmitters.

Applicant notes that the present claims describe treatment of "a subject having neurotrauma" or neuronal injury. Given the teachings of Grilli et al., Bakhshi et al. and Myseros et al. regarding prevention of damage, Applicant submits that one of skill in the art would not have a reasonable expectation of success using an NSAID in a method including administering to a subject having neurotrauma or neuronal injury. Thus, Applicant submits that no *prima facie* case of obviousness is established because, again, there is no expectation of success given the combined teachings of Grilli et al. and Myseros et al. Further, the Bakhshi et al. reference does not make up for the lack of such teachings since this reference is asserted only for the teaching of routes of administration to the CNS.

In view of the above remarks, reconsideration and the withdrawal of the rejection of claims 1, 5-7, 29-30, 32-36 and 38-40 under 35 U.S.C. §103(a) over Grilli et al. in view of Bakhshi et al. and further in view of Myseros et al. is solicited.

Remarks Directed to Rejection of Claims 4, 31, 37 and 41-42 Under 35 U.S.C. §103(a) Over Grilli et al. in View of Bakhshi et al. and Myseros et al. and Further in View of McGeer et al.

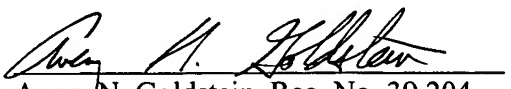
Applicant submits that this rejection is improper for the reasons detailed above and in the previous response. Applicant hereby incorporates by reference the above and previous remarks with regard to the deficiencies of Bakhshi et al. and Myseros et al. McGeer et al. fails to bolster Bakhshi et al. and Myseros et al. with regard to the limitations detailed. Additionally, claims 4, 31 and 37 are submitted to be patentable as the result of dependency from an allowable base claim.

On the basis of the above remarks, reconsideration and withdrawal of the rejection as to claims 4, 31, 37 and 41-42 under 35 U.S.C. §103(a) over Grilli et al. in view of Bakhshi et al. and Myseros et al. and in further view of McGeer et al. is solicited.

Summary

Claims 1, 4-7 and 29-42 are the claims pending in this application. Each claim is believed to be in proper form and directed to allowable and patentable subject matter. Reconsideration and allowance of the claims is requested. Should the Examiner find to the contrary, he is respectfully requested to contact the undersigned attorney in charge of this application to resolve any remaining issues.

Respectfully submitted,



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Gayna Lee

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